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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,096	01/08/2001	Lloyd G. Mitchell	A31304-B-A-B	5647

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,096	MITCHELL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *27-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on 12/08/03 is acknowledged. The traversal is on the ground(s) that the relationship between the subject matter encompassed by Groups I and II, there would not be an undue search burden to examine the pending claims as a single group. The examiner agrees to rejoin groups I and II, corresponding to claims 1-26 to be examined as a single invention. However, Applicants do not provide any specific arguments regarding the restriction of the remaining invention groups III-V. The restriction of groups III-V, drawn to claims 27-53 are considered proper for the reasons set forth in the restriction requirement of 6/03/2003, wherein it was previously stated:

> A. Inventions II and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, although the claimed methods comprise similar objectives, these methods comprise the use of chemically distinct nucleic acid molecules, which comprise distinct structures, and possess different modes of operation.
>
> B. Invention V is unrelated to invention II and IV since the nucleic acid molecule of invention V is not disclosed as being capable of use in the methods according to inventions II and IV. Inventions II and IV require the use of nucleic acid molecules comprising a structure according to either Invention I or III. The nucleic acid molecule according to Invention V is structurally distinct from both Invention I and III, therefore it is not immediately apparent that the nucleic acid molecules of Inventions I and III can be substituted by Invention V to be used in the methods set forth in Inventions II and IV.
>
> C. Inventions I, III and V are unrelated since they are drawn to chemically and structurally distinct nucleic acid molecules. The nucleic acid molecules of Inventions I and III represent trans-splicing cassettes that are useful for trans-splicing a gene of interest. However, Inventions I and III comprise different splicing components, and therefore possess different modes of operation. The nucleic acid molecule of Invention V represents a gene that encodes CFTR PTM24 and does not represent a trans-splicing cassette suitable for cloning a gene of interest as inventions IIII and I.
>
> D. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

For these reasons, the restriction of remaining invention groups III-V is still deemed proper and is therefore made FINAL.

2. Claims 27-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/08/03.

3. Claim 26 was rejoined to the elected invention since the claims was improperly separated into invention group III, the claims should have been included in invention group I since the claim depends from claim 1.

Priority

4. On page 1 of the specification as filed, Applicants improperly state that the filing date of provisional application number 60/008,317 is 12-15-1995. According to PTO records the filing date should state 12-07-1995.

Specification

5. The substitute specification filed 12/27/01 has not been entered because it does not conform to 37 CFR 1.125(b) and (c) because: ***the statement as to a lack of new matter under 37 CFR 1.125(b) is missing.***.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does not reasonably provide enablement for producing a chimeric mRNA in a cell *in vivo* for therapeutic treatment of conditions associated with the cystic

fibrosis trans-membrane conductance regulator (CFTR) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The instant claims read on a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of

the nucleic acid molecule to a CFTR pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The specification as filed provides only sufficient guidance and/or instruction for using the claimed nucleic acid constructs to produce chimeric within a cell in an *in vitro* environment, wherein said constructs are used to produce a chimeric mRNA. However, the specification as filed does not provide sufficient guidance such that the ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the compounds of the instant claims to treat conditions associated with defects in the coding region of the CFTR gene, in a method of gene therapy.

There are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within

the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated. Additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs that would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

It is noted that the instant application claims priority back to 12/15/1995, and that at the time the invention was made the state of the prior art indicated that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (Science, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "'[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page 1055, column 2).

To date, scientists still conclude that significant challenges remain before there is an actual "realistic prospect of a clinically effective" gene therapeutic treatment of cystic fibrosis (see Tate et al., 2005). According to Tate et al. (2005), "numerous obstacles including vector toxicity, inefficient transgene

expression and limited vector production have delayed progress." Tate et al. (2005) also mentions several barriers associated with airway gene therapy. For example, any method of airway delivery of a gene therapeutic agent (GTA) requires that the GTA get past a number of innate defense mechanisms specifically designed to prevent the entry of foreign particles. The mucous layer lining the airways is a natural barrier against viral and bacterial infection that can trap vectors, which are then removed by mucocilliary clearance or engulfed by macrophages. Beneath the mucous layer the complex glycocalyx can physically obstruct vectors and prevent binding to cell surface receptors. Furthermore, if the GTA reaches the apical cell membrane of the airway cells, there is a paucity of viral and growth tropic receptors to facilitate cell entry. Epithelial tight junctions further prevent vectors from reaching the basolateral membrane where receptors are present in greater abundance. After summarizing the various barriers associated with the treatment of cystic fibrosis using gene therapy, Tate concluded that "expression of biologically relevant CFTR transgene in the correct cells at the correct level with the duration to reconstitute normal physiology and innate immunity in the CF lung will be difficult.." (see Tate et al. page 276, Section #7).

In the instant case, the specification as filed does not provided sufficient guidance and/or instruction that would instruct the skilled artisan regarding how to overcome the known limitations associated with the treatment of cystic fibrosis comprising the use of a gene therapeutic approach as stated above. The quantity of experimentation required to practice the claimed invention would

encompass determining means such that all pre-trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the invention was made provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the CFTR gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

8. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Claims 1-26 are drawn to nucleic acid molecules, expression vectors and cells comprising said nucleic acid molecules, and methods for expressing said nucleic acid molecules in cells. The nucleic acid molecules of the invention comprise one or more target binding domains that target binding of the nucleic acid molecule to a generic pre-mRNA target or to a CFTR pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract, a 3' splice acceptor site and a 5' splice donor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell.

The specification as filed, see Figures 42-43, provide the coding sequence for exons 1-10 of the CFTR gene, modified codons in exon 10 are underlined and bold (Figure 42), the 153 base-pair nucleotide sequence of the PTM 24 Binding Domain (Figure 43A), and the complete sequence of CFTR PTM 24 (3' exon replacement PTM) showing the trans-splicing domain (underlined) and the coding sequence for exons 10-24 (Figure 43B). However, the specification as filed does not teach the skilled artisan how to predict the structures of the full

scope of "target binding domains" encompassed by the claims. According to the specification as filed, the CFTR pre-mRNAs of the invention encompass mRNAs isolated from all species of CFTR, including but not limited to mammalian CFTR. Additionally, see page 19, lines 14-21, which state that the CFTR target pre-mRNA is expressed within a specific cell type thereby providing a means for targeting expression of the novel chimeric RNA to a selected cell type. Therefore, apart from further experimentation, the skilled artisan would not be able to predict the actual structural description of the full scope of target binding domains that target binding of the nucleic acid molecules of the invention to a CFTR pre-mRNA encompassed by the instant claims.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying

characteristics sufficient to show that applicant was in possession of the claimed invention."

Moreover, according to MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." In the instant case, the specification as filed does not provide an adequate description of the target binding domains of the invention, wherein said target binding domains target binding of the nucleic acid molecules of the invention to a CFTR pre-mRNA other than the CFTR target domains described in Figures 42-43 of the instant specification as filed, because CFTR pre-mRNA are cell-type specific as stated by Applicants on page 19 of the specification as filed.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim(s) 1-5, 8-14, 17-19, 22-24, and 26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,013,487. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims and claims 1-34 of U.S. Patent No. 6,013487 are both directed to a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a target pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The instant claims are drawn to wherein the nucleic acid molecules comprise a 5' splice donor site, and wherein there is a spacer region that separates the 5' splice donor site and/or the 3' splice site and the 5' splice donor from the target

binding domains. This aspect of the instant claims is considered an obvious variation of the issued claims, since issued claim 2, limits the nucleic acid of issued claim 1, to comprise a 5' splice donor site. Issued claim 1 comprises one or more target binding domains, a 3' splice region, a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA. Issued claim 2 limits the nucleic acid of claim 1 to further comprise a 5' splice donor site. Although the issued claims do not recite that the issued nucleic acids comprise wherein the 5' splice donor site is separated from the target binding domains by a spacer region, the issued claims are disclosed as "comprising" a 5' splice donor site, therefore separating the 5' splice donor region from the target binding domain by a spacer region would be considered an obvious variation based upon issued claim 9, 12, and 20 which are drawn to a nucleic acid comprising a 5' splice site separated from the target binding domain by a spacer region.

11. Claims 1-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 6,280,978 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the issued claims and the pending claims are drawn to nucleic acids, cells comprising said nucleic acids, and methods comprising the use of said nucleic acid molecules, wherein said nucleic acid molecules comprise one or more target binding domains, a 3' splice region, a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer

region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA. Issued claim 4 limits the nucleic acid of claim 1 to further comprise a 5' splice donor site. Although the issued claims do not recite that the issued nucleic acids comprise wherein the 5' splice donor site is separated from the target binding domains by a spacer region, the issued claims are disclosed as "comprising" a 5' splice donor site, therefore separating the 5' splice donor region from the target binding domain by a spacer region would be considered an obvious variation based upon issued claims 3, 11, 15, 20, and 30 which are drawn to a nucleic acid molecules (vectors or methods comprising the use of said nucleic acid molecules) comprising a 5' splice site separated from the target binding domain by a spacer region.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
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JLE